

Compound	Name	Structure
P1	6,6-Bis-(4-fluoro-phenyl)-1-[4-(2-phenylsulfanyl-ethyl)-piperazin-1-yl]-hexan-1-one	
P2	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(4-fluoro-phenoxy)-ethyl]-piperazine	
P3	1-{4-[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P4	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(2-phenylsulfanyl-ethyl)-piperazine	
P5	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(4-methoxy-phenoxy)-ethyl]-piperazine	

Figure 1

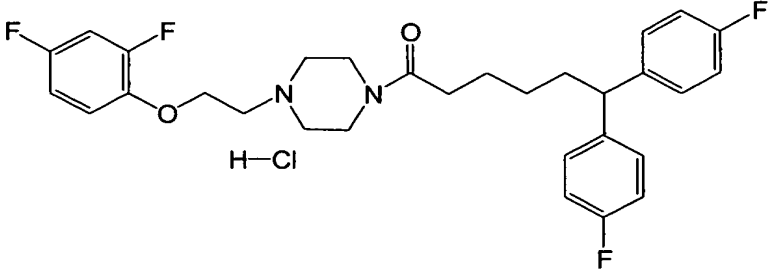
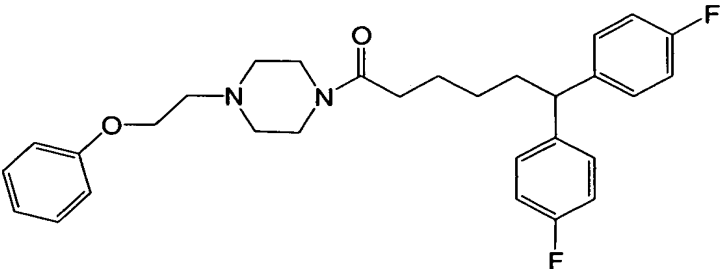
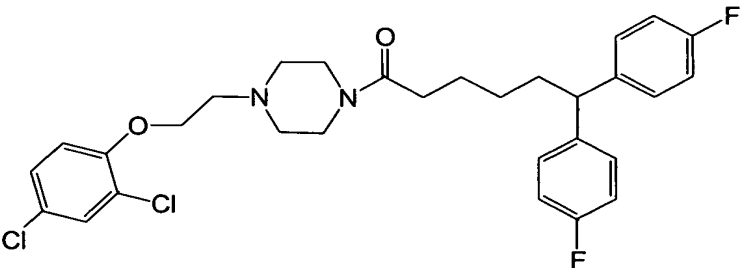
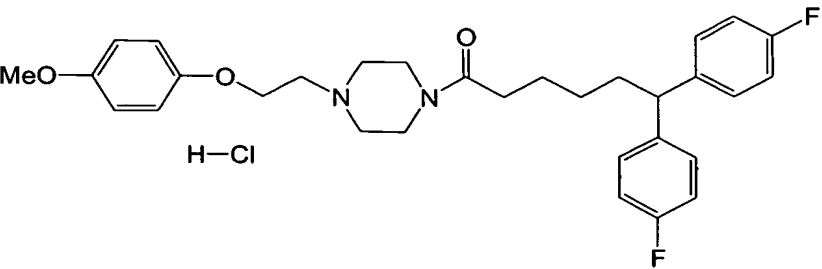
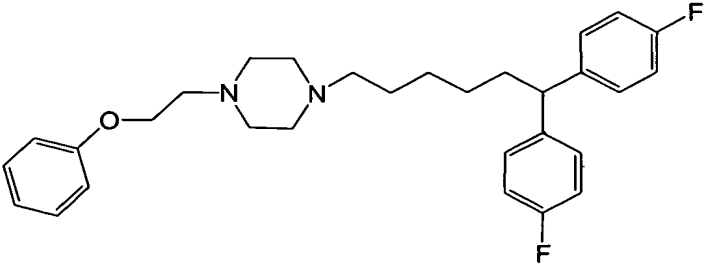
Compound	Name	Structure
P6	1-{4-[2-(2,4-Difluorophenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P7	6,6-Bis-(4-fluoro-phenyl)-1-[4-(2-phenoxy-ethyl)-piperazin-1-yl]-hexan-1-one	
P8	1-{4-[2-(2,4-Dichlorophenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P9	6,6-Bis-(4-fluoro-phenyl)-1-{4-[2-(4-methoxyphenoxy)-ethyl]-piperazin-1-yl}-hexan-1-one	
P10	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(2-phenoxy-ethyl)-piperazine	

Figure 1

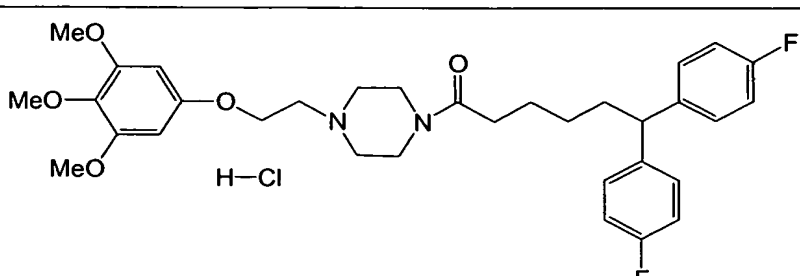
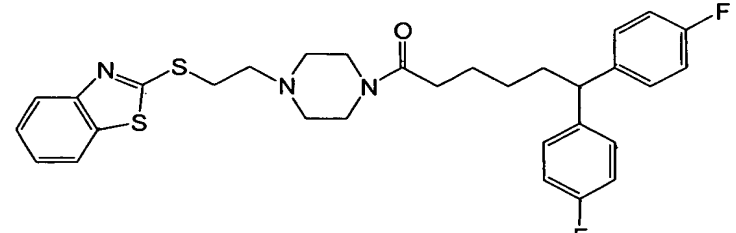
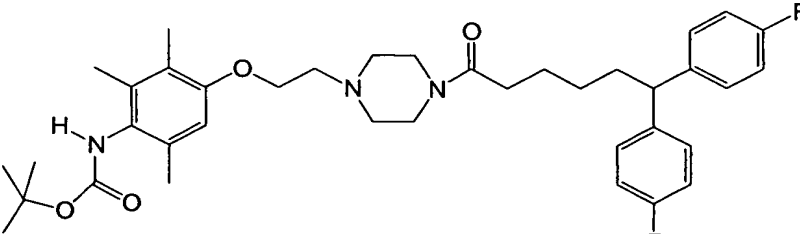
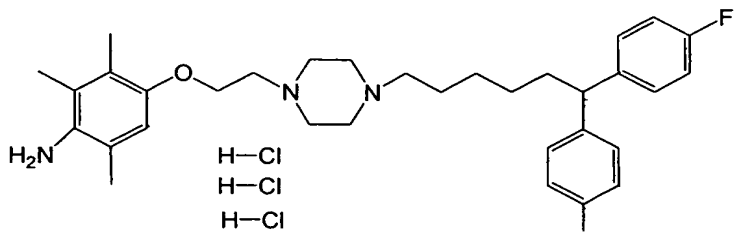
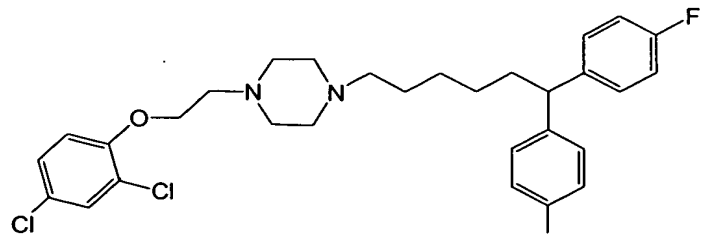
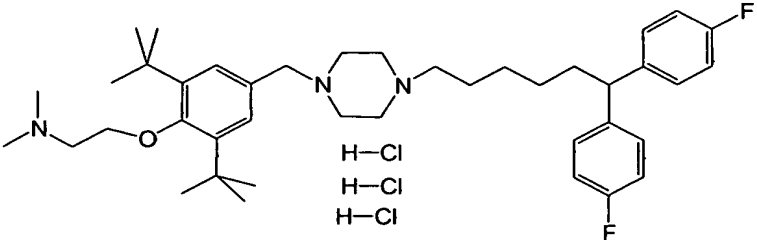
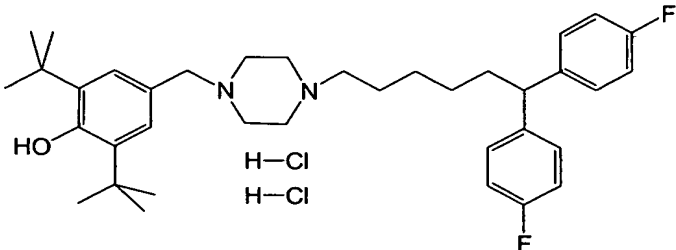
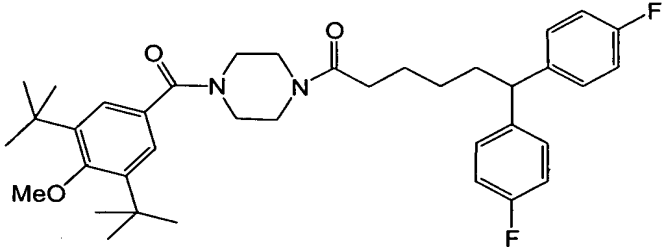
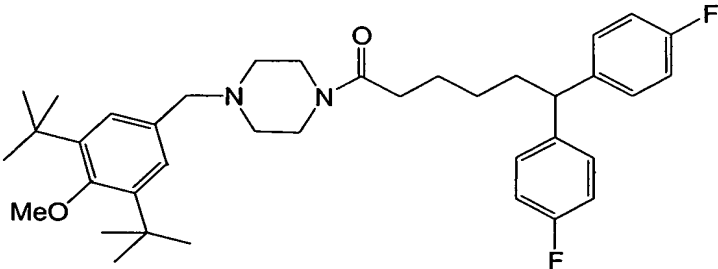
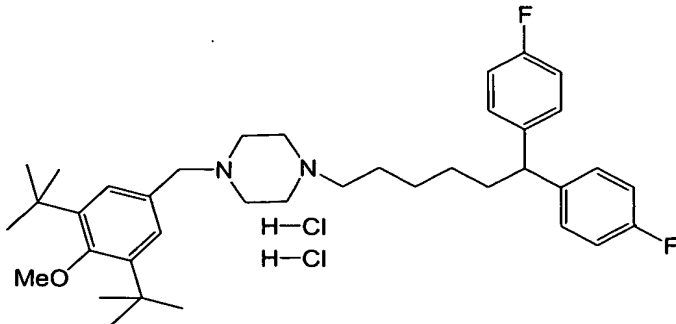
Compound	Name	Structure
P11	6,6-Bis-(4-fluoro-phenyl)-1-{4-[2-(3,4,5-trimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-hexan-1-one	
P12	1-{4-[2-(Benzothiazol-2-ylsulfanyl)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P13	[4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenyl]-carbamic acid tert-butyl ester	
P14	4-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethoxy)-2,3,6-trimethyl-phenylamine	
P15	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(2,4-dichloro-phenoxy)-ethyl]-piperazine	

Figure 1

Compound	Name	Structure
P16	[2-(4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenoxy)-ethyl]-dimethyl-amine	
P17	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-di-tert-butyl-phenol	
P18	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P19	1-[4-(3,5-Di-tert-butyl-4-methoxy-benzyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P20	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazine	

**Figure 1**

Compound	Name	Structure
P21	{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-methoxy-phenyl)-methanone	
P22	1-{4-[3,5-Di-tert-butyl-4-(2-dimethylamino-ethoxy)-benzoyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P23	1-Benzo[1,3]dioxol-5-ylmethyl-4-[6,6-bis-(4-fluoro-phenyl)-hexyl]-piperazine	
P24	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,5-di-tert-butyl-benzyl)-piperazine	
P25	{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-(3,5-di-tert-butyl-4-hydroxy-phenyl)-methanone	

Figure 1

Compound	Name	Structure
P26	1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P27	1-[4-(3,5-Dibromo-4-hydroxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P28	1-[4-(3,5-Di-tert-butyl-4-hydroxy-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P29	1-[4-(3,5-Di-tert-butyl-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P30	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(4-tert-butyl-benzyl)-piperazine	

**Figure 1**

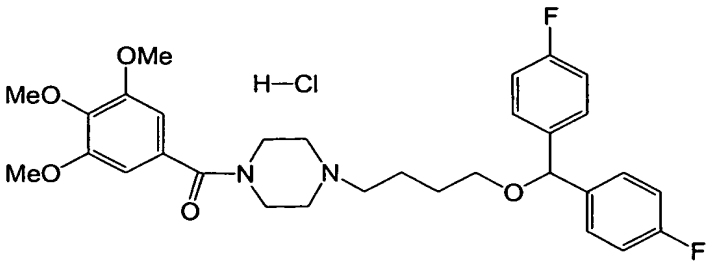
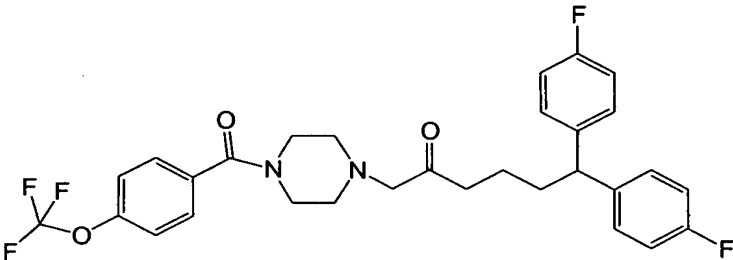
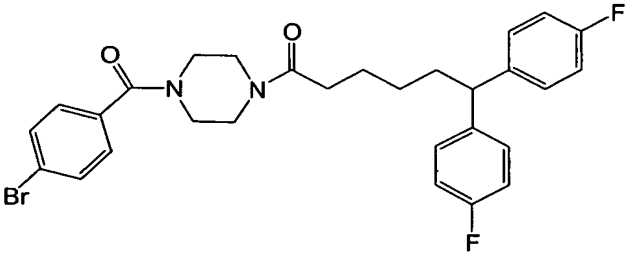
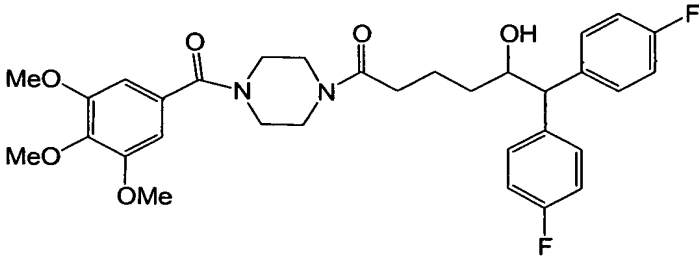
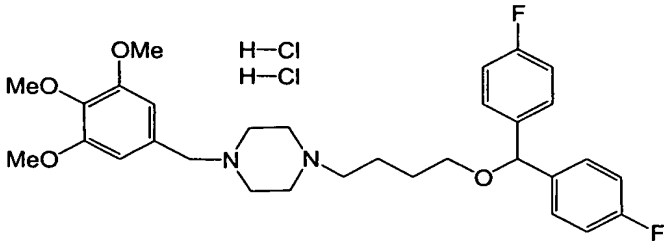
Compound	Name	Structure
P31	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(9H-thioxanthen-9-yl)-piperazine	
P32	2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-benzothiazole	
P33	6,6-Bis-(4-fluorophenyl)-1-(4-pyrimidin-2-yl)-piperazin-1-yl-hexan-1-one	
P34	2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-pyrimidine	
P35	6,6-Bis-(4-fluorophenyl)-1-[4-(9H-thioxanthen-9-yl)-piperazin-1-yl]-hexan-1-one	

**Figure 1**

Compound	Name	Structure
P36	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid ethyl ester	
P37	6,6-Bis-(4-fluoro-phenyl)-1-{4-[2-(3,4,5-trimethoxy-benzylamino)-ethyl]-piperazin-1-yl}-hexan-1-one	
P38	9,9-Bis-(4-fluoro-phenyl)-1-[4-(3,4,5-trimethoxy-benzyl)-piperazin-1-yl]-nonan-1-one	
P39	(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-phenyl-amine	
P40	1-[9,9-Bis-(4-fluoro-phenyl)-nonyl]-4-(3,4,5-trimethoxy-benzyl)-piperazine	

Figure 1



Compound	Name	Structure
P41	(4-{4-[Bis-(4-fluoro-phenyl)-methoxy]-butyl}-piperazin-1-yl)-(3,4,5-trimethoxy-phenyl)-methanone	
P42	6,6-Bis-(4-fluoro-phenyl)-1-[4-(4-trifluoromethoxy-benzoyl)-piperazin-1-yl]-hexan-2-one	
P43	1-[4-(4-Bromo-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P44	6,6-Bis-(4-fluoro-phenyl)-5-hydroxy-1-[4-(3,4,5-trimethoxy-benzoyl)-piperazin-1-yl]-hexan-1-one	
P45	1-{4-[Bis-(4-fluoro-phenyl)-methoxy]-butyl}-4-(3,4,5-trimethoxy-benzyl)-piperazine	

**Figure 1**

Compound	Name	Structure
P46	6,6-Bis-(4-fluoro-phenyl)-6-hydroxy-1-[4-(3,4,5-trimethoxy-benzoyl)-piperazin-1-yl]-hexan-1-one	
P47	4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazine-2-carboxylic acid	
P48	4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-1-(3,4,5-trimethoxy-benzyl)-piperazin-2-one	
P49	1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-4-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	
P50	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,4,5-trimethoxy-benzoyl)-piperazin-2-one	

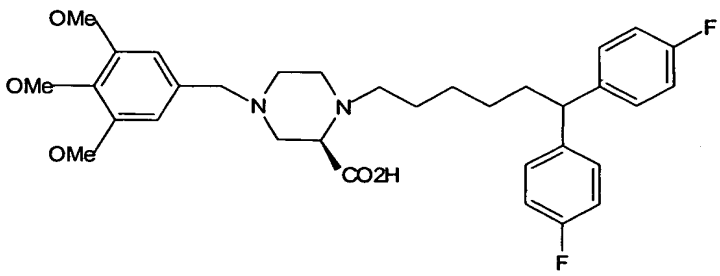
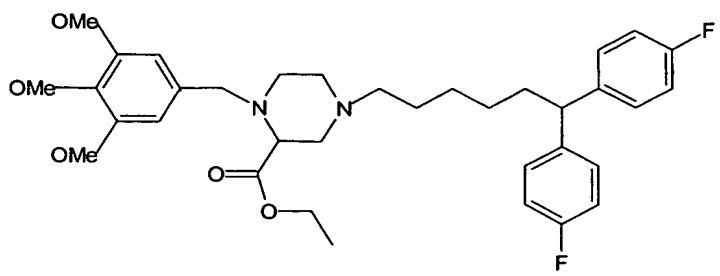
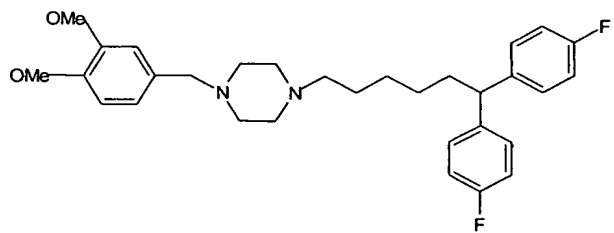
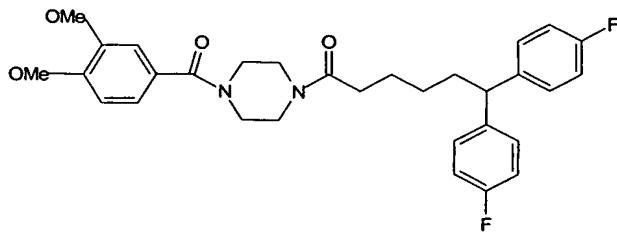
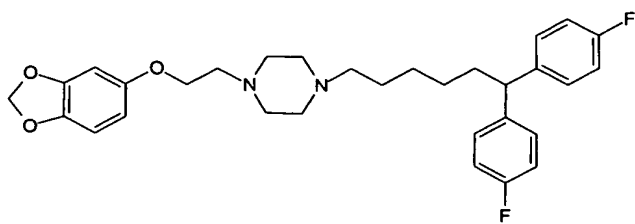
**Figure 1**

Compound	Name	Structure
P51	4-[6,6-Bis-(4-fluorophenyl)-hexyl]-1-(3,4,5-trimethoxy-benzyl)-piperazin-2-one	
P52	4-[6,6-Bis-(4-fluorophenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazin-2-one	
P53	4-[6,6-Bis-(4-fluorophenyl)-hexanoyl]-1-[2-(4-fluorophenoxy)-ethyl]-piperazin-2-one	
P54	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	
P55	4-[6,6-Bis-(4-fluorophenyl)-hexanoyl]-1-(3,5-di-tert-butyl-4-methoxy-benzoyl)-piperazin-2-one	

Figure 1

Compound	Name	Structure
P56	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(3,5-di-tert-butyl-4-methoxy-benzyl)-piperazin-2-one	
P57	1-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-4-(3,5-di-tert-butyl-4-hydroxy-benzoyl)-piperazin-2-one	
P58	6,6-Bis-(4-fluoro-phenyl)-1-[4-(3,4,5-trimethoxy-benzoyl)-piperazin-1-yl]-hex-5-en-1-one	
P59	1-{4-[2-(3,4-Dimethoxy-phenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P60	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-[2-(3,4-dimethoxy-phenoxy)-ethyl]-piperazine	

Figure 1

Compound	Name	Structure
P61	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(3,4,5-trimethoxybenzyl)-piperazine-2-carboxylic acid	
P62	4-[6,6-Bis-(4-fluorophenyl)-hexyl]-1-(3,4,5-trimethoxybenzyl)-piperazine-2-carboxylic acid ethyl ester	
P63	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(3,4-dimethoxybenzyl)-piperazine	
P64	1-[4-(3,4-Dimethoxybenzoyl)-piperazin-1-yl]-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P65	1-[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-4-[6,6-bis-(4-fluorophenyl)-hexyl]-piperazine	

**Figure 1**

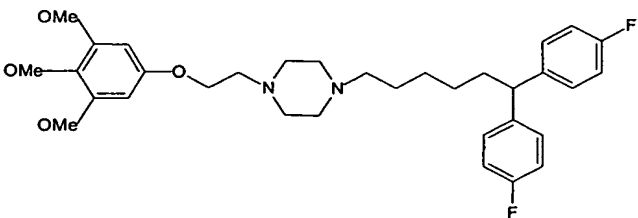
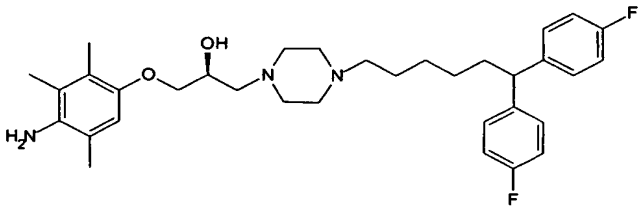
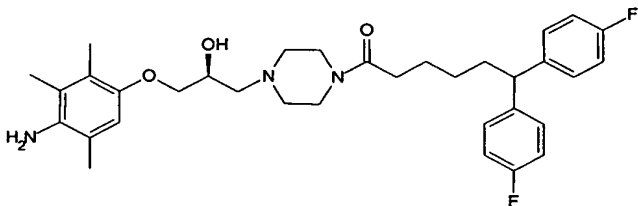
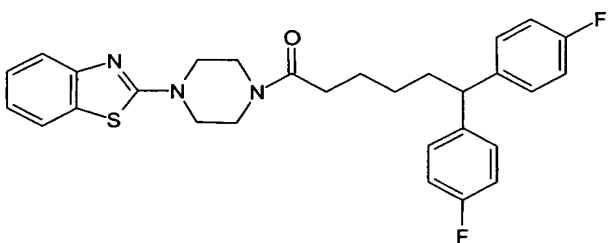
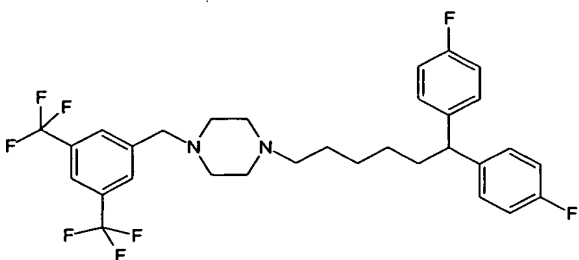
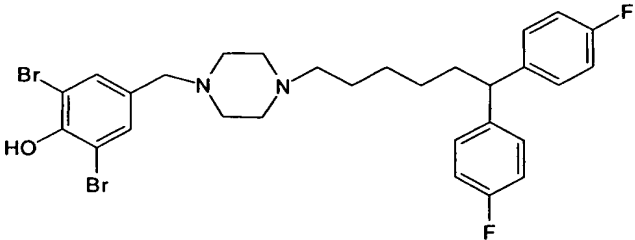
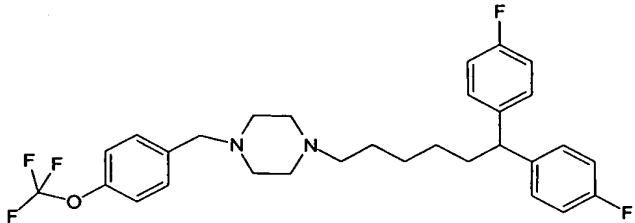
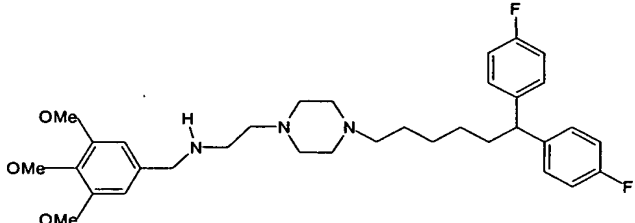
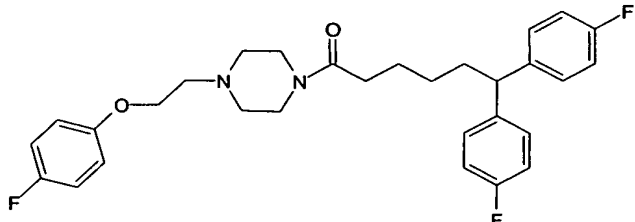
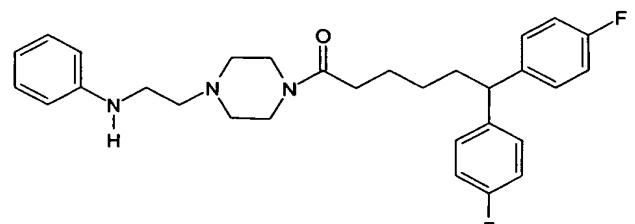
Compound	Name	Structure
P66	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-[2-(3,4,5-trimethoxyphenoxy)-ethyl]-piperazine	
P67	1-(4-Amino-2,3,5-trimethyl-phenoxy)-3-{4-[6,6-bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-propan-2-ol	
P68	1-{4-[3-(4-Amino-2,3,5-trimethyl-phenoxy)-2-hydroxy-propyl]-piperazin-1-yl}-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P69	1-(4-Benzothiazol-2-yl-piperazin-1-yl)-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P70	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(3,5-bis-trifluoromethyl-benzyl)-piperazine	

Figure 1

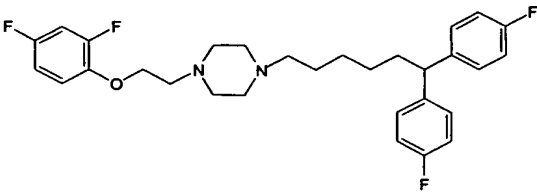
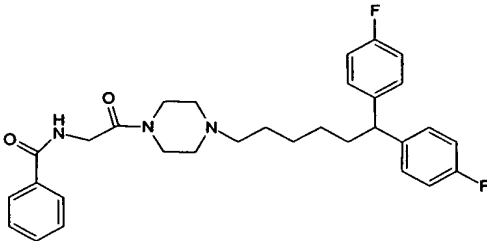
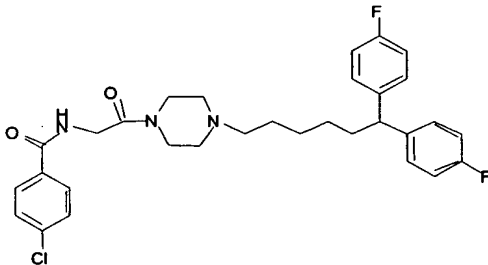
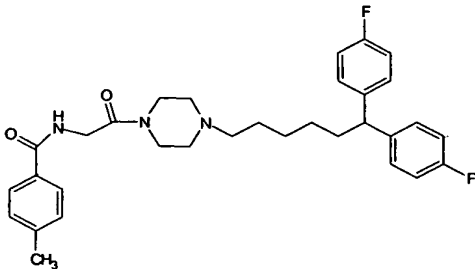
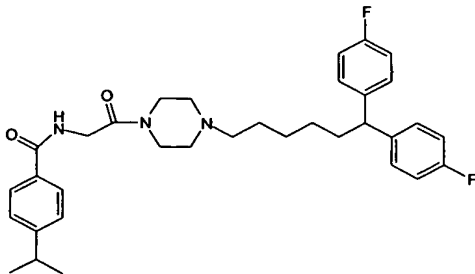
Compound	Name	Structure
P71	1-[4-(3,5-Bis-trifluoromethyl-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P72	1-[4-(4-tert-Butyl-benzoyl)-piperazin-1-yl]-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P73	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-(4-bromo-benzyl)-piperazine	
P74	2-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethylsulfanyl)-benzothiazole	
P75	6,6-Bis-(4-fluorophenyl)-1-[4-(4-hydroxy-3,5-dimethoxy-benzoyl)-piperazin-1-yl]-hexan-1-one	

**Figure 1**

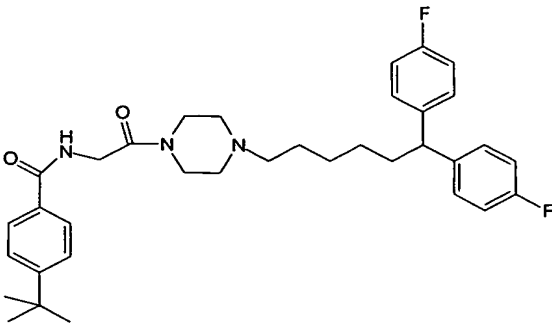
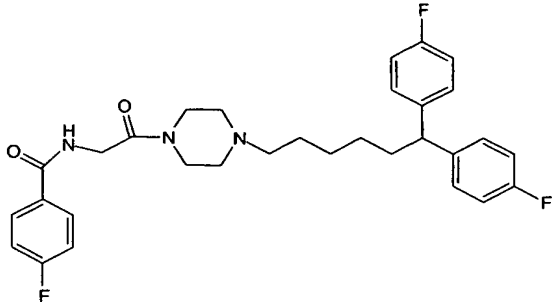
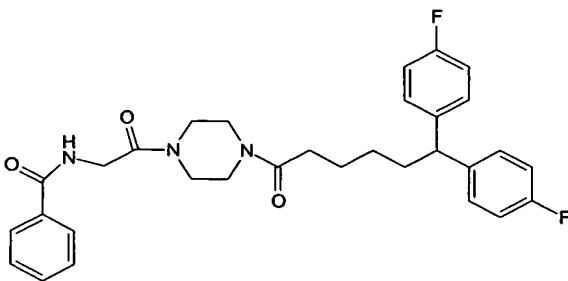
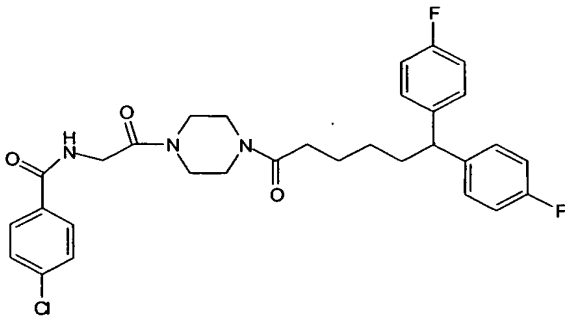
Compound	Name	Structure
P76	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dibromo-phenol	
P77	1-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-4-(4-trifluoromethoxy-benzyl)-piperazine	
P78	(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-ethyl)-(3,4,5-trimethoxy-benzyl)-amine	
P79	1-{4-[2-(4-Fluorophenoxy)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P80	6,6-Bis-(4-fluoro-phenyl)-1-[4-(2-phenylamino-ethyl)-piperazin-1-yl]-hexan-1-one	

**Figure 1**



Compound	Name	Structure
P81	1-[6,6-Bis-(4-fluorophenyl)-hexyl]-4-[2-(2,4-difluorophenoxy)-ethyl]-piperazine	
P82	N-(2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-benzamide	
P83	N-(2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-4-chlorobenzamide	
P84	N-(2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-4-methylbenzamide	
P85	N-(2-{4-[6,6-Bis-(4-fluorophenyl)-hexyl]-piperazin-1-yl}-2-oxoethyl)-4-isopropylbenzamide	

**Figure 1**

Compound	Name	Structure
P86	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-tert-butyl-benzamide	
P87	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide	
P88	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-benzamide	
P89	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-chloro-benzamide	

**Figure 1**

Compound	Name	Structure
P90	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-methyl-benzamide	
P91	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-isopropyl-benzamide	
P92	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-tert-butyl-benzamide	
P93	N-(2-{4-[6,6-Bis-(4-fluoro-phenyl)-hexanoyl]-piperazin-1-yl}-2-oxo-ethyl)-4-fluoro-benzamide	

**Figure 1**

Compound	Name	Structure
P94	1-[4-(2-Benzylamino-ethyl)-piperazin-1-yl]-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P95	1-{4-[2-(4-Chlorobenzylamino)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluorophenyl)-hexan-1-one	
P96	6,6-Bis-(4-fluorophenyl)-1-{4-[2-(4-methylbenzylamino)-ethyl]-piperazin-1-yl}-hexan-1-one	
P97	6,6-Bis-(4-fluorophenyl)-1-{4-[2-(4-isopropylbenzylamino)-ethyl]-piperazin-1-yl}-hexan-1-one	

**Figure 1**

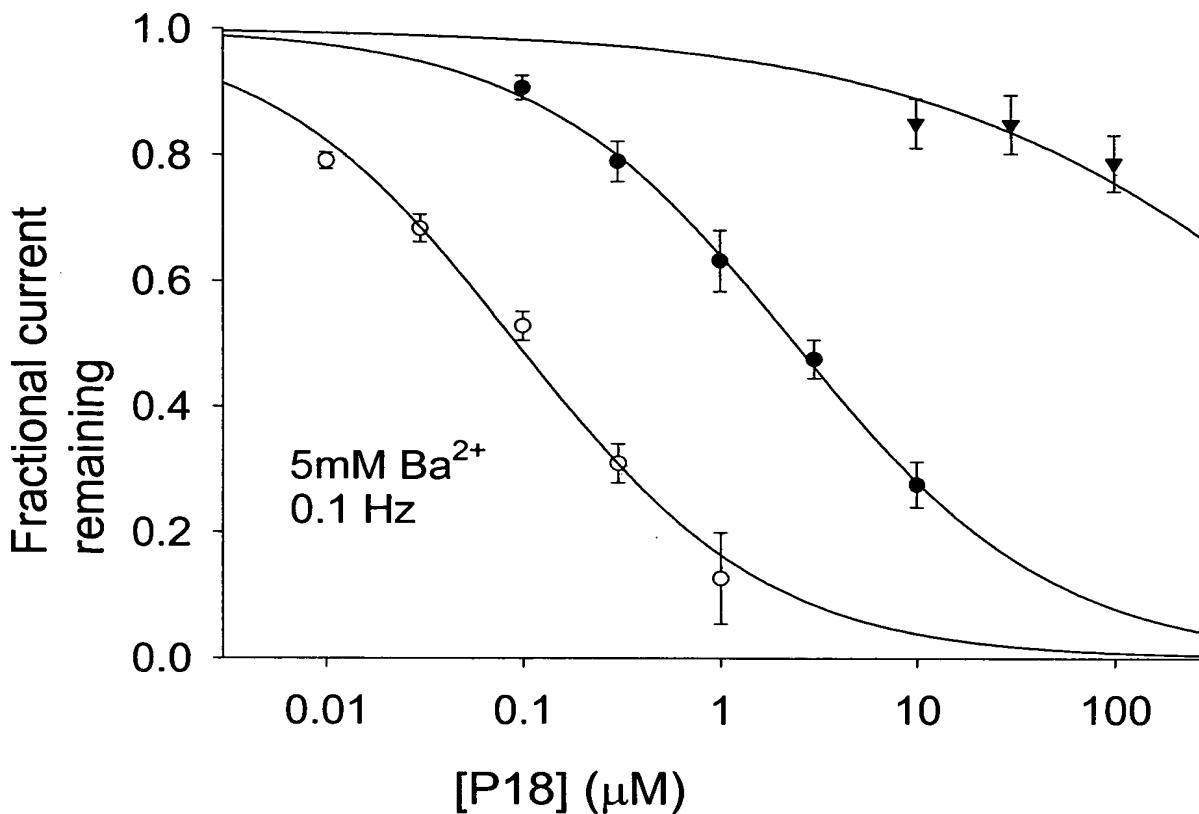
Compound	Name	Structure
P98	1-{4-[2-(4-tert-Butyl-benzylamino)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P99	1-{4-[2-(4-Fluoro-benzylamino)-ethyl]-piperazin-1-yl}-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P100	6,6-Bis-(4-fluoro-phenyl)-1-[4-(1-hydroxy-pyridine-4-carbonyl)-piperazin-1-yl]-hexan-1-one	
P101	4-{4-[6,6-Bis-(4-fluoro-phenyl)-hexyl]-piperazin-1-ylmethyl}-2,6-dimethoxy-phenol	

**Figure 1**

Compound	Name	Structure
P102	9,9-Diphenyl-1-[4-(3,4,5-trimethoxybenzyl)-piperazin-1-yl]-nonan-1-one	
P103	1-[4-(3,5-Di-tert-butyl-4-methoxybenzoyl)-2-methylpiperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P104	1-[4-(3,5-Di-tert-butyl-4-methoxybenzoyl)-3-methylpiperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P105	1-[4-(3,5-Di-tert-butylbenzoyl)-2-methylpiperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	
P106	1-[4-(4-tert-Butylbenzoyl)-2-methylpiperazin-1-yl]-6,6-bis-(4-fluoro-phenyl)-hexan-1-one	

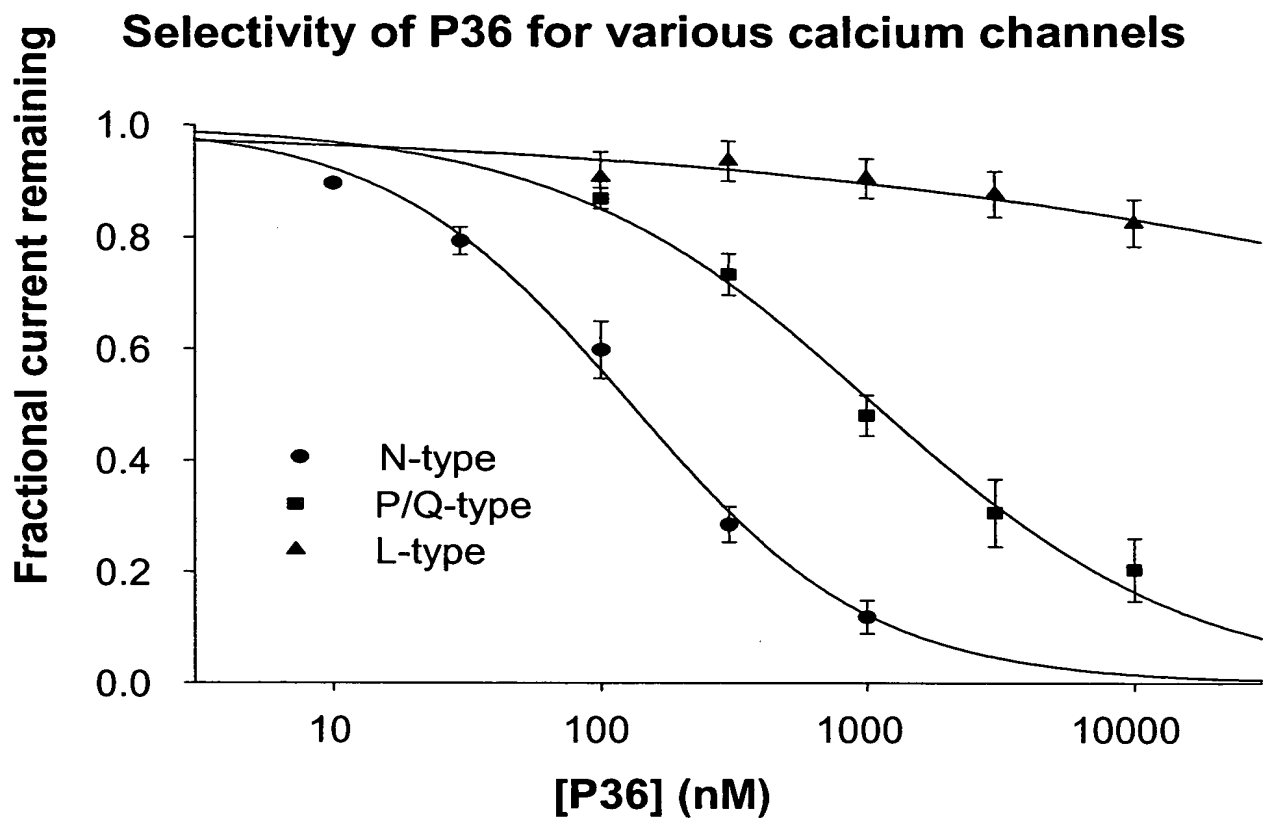
**Figure 1**

## Selectivity of P18 for various calcium channels



- N-type  $IC_{50} = 0.11 \pm 0.02 \mu M$  (n=5)
- P/Q-type  $IC_{50} = 2.71 \pm 0.28 \mu M$  (n=5)
- ▼ L-type  $IC_{50} >> 100 \mu M$  (n=5)

Figure 2



N-type IC<sub>50</sub> = 136 ± 13 nM (n=6)

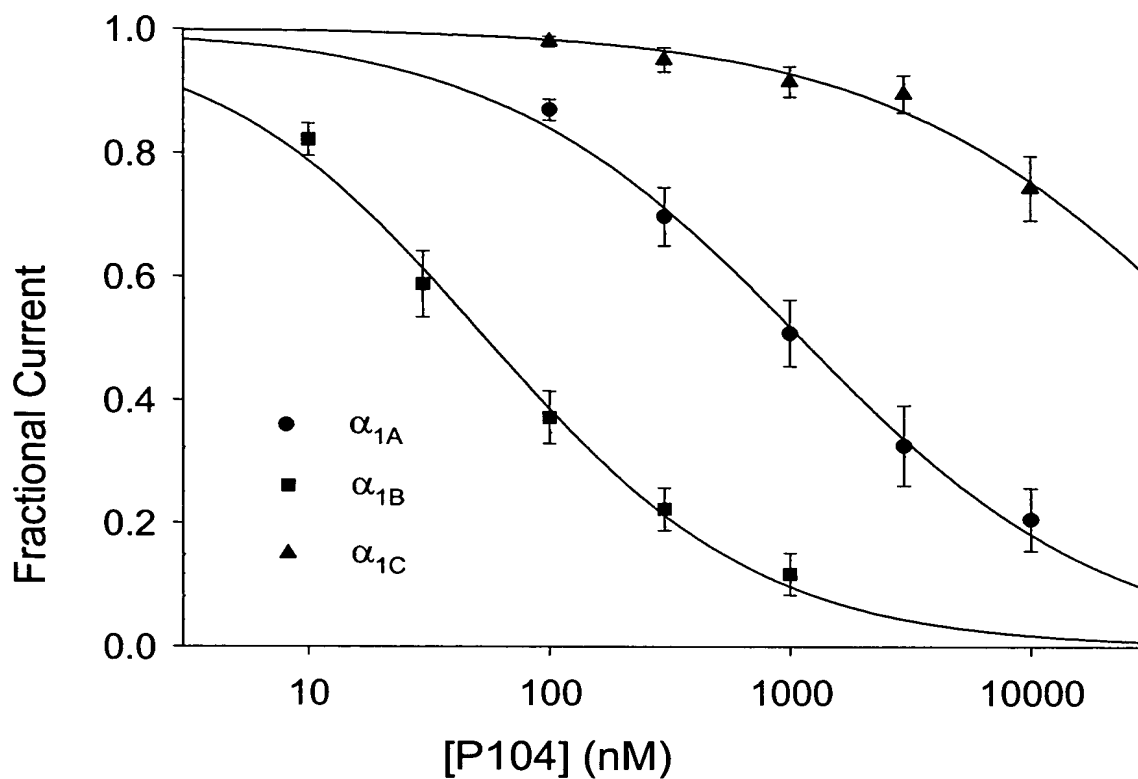
P/Q-type IC<sub>50</sub> = 920 ± 123 nM (n=5)

L-type IC<sub>50</sub> >>> 10 μM (n=5)

**Figure 3**



## Effect of P104 on Various HVA $\text{Ca}^{2+}$ Channels



P/Q-type  $\text{IC}_{50} = 1659 \pm 811 \text{ nM}$  (n=5)

N-type  $\text{IC}_{50} = 61 \pm 11 \text{ nM}$  (n=5)

L-type  $\text{IC}_{50} >> 10 \mu\text{M}$  (n=5) (estimate :  $144 \mu\text{M}$ )

**Figure 4**